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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Liang Li

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CHRISTIE, PARKER & HALE, LLP
PO BOX 7068
PASADENA, CA 91109-7068

EXAMINER

NATARAJAN, MEERA

ART UNIT

PAPER NUMBER

1643

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/565,751	Applicant(s) LI ET AL.	
	Examiner MEERA NATARAJAN	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 1,2 and 6-9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3-5 and 10-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendments in the reply filed on 12.26.2008 is acknowledged and entered into the record.
2. Accordingly, Claims 1-23 are pending. Claims 1, 2, 6-9 are withdrawn as being drawn to non-elected inventions.
3. Claims 3-5 and 10-23 will be examined on the merits.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
 1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
6. Claims 3-5 and 10-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (Acta Pharmaceutica Sinica, Vol. 35, No.7, pp.488-491, 2000) in view of Terpe et al. (Appl. Microbiol. Biotechnol., Vol. 60, pp.523-533, epub Nov. 2002), Kortt et

Art Unit: 1643

al. (Biomol Eng, Vol. 18(3), 2001) and Mierendorf et al. (Newsletter of Novagen, Vol 1, No 1, 1994).

7. The claim is drawn to a method of producing an energized fusion protein Fv-LDP-AE consisting of a fusion protein Fv-LDP that contains the single-chain Fv fragment (scFv) of monoclonal antibody against type IV collagenase, the apoprotein of lidamycin (LDP), the flexible spacer GGGGS between scFv and LDP, and a C-terminal His₆-tag and an active enediyne chromophore (AE) that derives from lidamycin.

8. Li et al teach engineering and assembling a fusion protein consisting of a enediyne chromophore of lidamycin (see Fig.1 and materials and methods) and a recombinant fusion protein LDP-Fv which comprises a scFv antibody against type IV collagenase, lida-protein(LDP) and the spacer GGGGS between them. Li et al. teach anti-invasion activity of the LDP-Fv fusion protein in lung cancer PG cells (see Fig. 5). Li et al. does not teach a His₆-tag or the use of pET-30a. These deficiencies are made up for by Terpe et al., Kortt et al., Mierendorf et al.

9. Terpe et al. teach proteins containing a tag to facilitate the purification of the target polypeptides are widely used. Terpe et al. disclose several tags such as FLAG-tag, HAT-tag, His-tag, Strep-tag and S-tag (see abstract).

10. Kortt et al. teach a number of cancer targeting scFv fusion proteins that have undergone successful pre-clinical trials for in vivo stability and efficacy engineered in various orientations.

Art Unit: 1643

11. Mierendorf et al. teach the use of the pET expression system is used to achieve high expression and best possible yields of a protein through its vector/host combinations.

12. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use a His-tag as taught by Terpe et al. to help in the purification of the fusion protein taught by Li et al. and to use the pET expression system to obtain the high yield percentages claimed. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the teachings of Li et al., Terpe et al. and Mierendorf et al., because Terpe et al. teach tag, specifically His-tags, facilitate purification of the target polypeptides and are most commonly used and Mierendorf et al. teach the pET system can achieve high protein yields. Additionally, one of ordinary skill in the art would have been motivated to make a fusion protein in the orientation recited in the claims based on the teachings of Kortt et al. that several different orientations can still achieve successful in vivo results for cancer therapy. Although Li et al. is silent in regards to the percentage of enediyne chromophore (AE), the fusion protein was used in an anti-invasion assay of lung cancer cells and therefore one of ordinary skill in the art would be motivated to optimize the percentage of AE by routine experimentation in order to achieve the best cytotoxicity because Li et al. teach use of the fusion protein in cancer therapy.

Response to Arguments

13. Applicants argue the orientation of the fusion protein taught by Li et al. is different that the fusion protein claimed in the instant application. Applicants argue the position

Art Unit: 1643

of the components has a profound effect on the folding and action of the individual components. In addition applicants argue Li et al. does not disclose a high protein yield as claimed in the instant application or the use of the pET-30a expression plasmid.

These arguments have been carefully considered but not found persuasive. Applicants have provided no evidence that the different orientation of the Li et al. fusion protein is what contributes to the decreased cytotoxicity. In fact, applicants point out the different in cytotoxicity of a fusion protein without AE to one with AE. One of ordinary skill in the art could argue the decreased cytotoxicity is due to the absence of AE and is not due to the different orientation of the fusion protein. Applicants have not provided substantial evidence that the fusion protein taught by Li et al. is less cytotoxic due to its orientation.

It is also obvious to one of ordinary skill in the art to use different expression systems and plasmids to optimize protein yield. Therefore it would have been obvious to one of ordinary skill in the art to use an expression vector system to produce the highest yield possible, such as with the pET system as described in Mierendorf et al. Applicants argue the only difference between the claimed method and that taught by Li et al. are the different orientation, difference in IC_{50} and the relative yield of the fusion protein. These differences are remedied by the references cited above.

All other objections/rejections are withdrawn in view of Applicants amendments to the claims.

Conclusion

14. Claims 3-5 and 10-23 are rejected

Art Unit: 1643

15. No Claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1643

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643